Pulmonary vascular disease is an important complication of portosystemic shunting in children and adults with chronic liver diseases and cirrhosis, extrahepatic portal vein obstruction/thrombosis or congenital portosystemic shunts (CPSSs). Two major types of pulmonary vascular disease in this context are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH), both of which may indicate the need for liver transplantation. The hallmark of HPS is intrapulmonary vascular dilatation (IPVD) and shunting leading to an increased alveolar-arterial gradient and, generally, hypoxemia (Table I). In contrast, POPH is characterized by progressive remodeling of the wall of small pulmonary arteries with vasoconstriction and/or vascular obstruction because of thickening of the arterial wall leading to pulmonary arterial hypertension (PAH) and right heart failure (Table I). Both HPS and POPH significantly impair the quality of life in affected children and are risk factors for mortality. Thus, patients with HPS and POPH are given exception model end-stage liver disease/pediatric end-stage liver disease points under United Network for Organ Sharing policy and are prioritized for liver transplantation because of their high pre- and postliver transplantation mortality. Current pharmacotherapies have not been proven to reverse either of these conditions in affected children. Liver transplantation, a life-saving procedure for irreversible chronic liver disease with end-stage liver disease or other serious complications, is indicated in patients with severe HPS. Generally, POPH by itself is not an indication for liver transplantation, but mild-to-moderate POPH may respond to liver transplantation if there is another indication for liver transplantation. In addition, medically treated POPH may safely facilitate an otherwise needed liver transplantation. However, the optimal timing of liver transplantation in these conditions in children has not been clearly defined.

Definitions and Diagnostic Criteria

Definitions

HPS is defined by the presence of the triad of IPVD and abnormal arterial oxygenation in the setting of advanced liver disease, portal hypertension, or CPSS (Table I). Although most cases of HPS are associated with advanced liver disease, the pathophysiologic features of HPS can also be seen in survivors of the Fontan procedure for single ventricle disease and with no pre-existing liver disease. Chronic venous hypertension after Fontan procedure may lead to liver congestion, fibrosis, and, eventually, pulmonary arteriovenous fistulas and HPS. Clinically, HPS is characterized by the presence of an increased age-corrected alveolar-arterial oxygen gradient on room air, with or without hypoxemia. The development of IPVD in HPS (detected by agitated saline contrast-enhanced transthoracic echocardiography) leads to an oxygenation defect in pulmonary capillaries and effective right to left shunting. Although advanced cirrhosis is the most common liver condition associated with HPS, it may also develop in noncirrhotic portal hypertension, CPSS, and ischemic hepatitis.

POPH is defined as PAH associated with portal hypertension either inferred clinically (from the presence of splenomegaly, thrombocytopenia, portosystemic shunts, esophageal varices, or portal vein abnormalities) or confirmed with hemodynamic measurements showing a raised mean pulmonary artery pressure (mPAP >25 mm Hg), increased pulmonary vascular resistance (>3 Wood units), and pulmonary artery wedge pressure <15 mm Hg (Table I).

Most of the studies on HPS in children have used the diagnostic criteria described by Donovan et al, with some modifications (Table II; available at www.jpeds.com). The European Cardiology Society/European Respiratory Society Joint Task Force on the Diagnosis and Treatment of Pulmonary Hypertension and the International Liver Transplant Society (ILTS) Practice Guidelines recommend uniform diagnostic criteria for both HPS and POPH (Table I), which will be helpful for future epidemiology studies and therapeutic trials.

Pathogenesis

The pathophysiology of HPS and POPH is shown in Figures 1 and 2. The hallmark of HPS is the presence of IPVD.
Characterized by diffuse or localized dilated abnormal pulmonary capillaries as well as arteriovenous communications. Three mechanisms are thought to play a role in the impaired oxygenation of venous blood as it flows through the pulmonary circulation: ventilation/perfusion (V’/Q’) mismatch, intrapulmonary shunting, and limitation of oxygen diffusion. Nitric oxide, a potent vasodilator, has been linked to IPVD. The pathogenesis of HPS is shown in Figure 2. Recent animal studies on the inhibition of pulmonary angiogenesis in HPS by placental growth factor may represent a novel strategy in the therapy for HPS. The pathophysiology of POPH is not fully understood, partially because of a lack of a suitable animal model as well as the rarity of the condition. Histologically, there is a similarity between POPH and PAH. Both are characterized by obstruction of pulmonary arterial blood flow caused by intimal proliferation, medial smooth muscle hypertrophy, fibrosis, and in situ thrombosis. This leads to a thickening of the arterial wall and blood vessel occlusion and, eventually, elevated pulmonary vascular resistance. A case-control study showed that POPH was associated with female sex, single nucleotide polymorphisms in genes involved in estrogen metabolism (estrogen receptor-1), and raised circulating estrogen levels, supporting the potential role of sex hormones in the pathogenesis of POPH. Other causes of PAH, which need to be considered include sleep apnea, chronic obstructive airway disease, and interstitial pulmonary fibrosis. A proposed mechanism for POPH suggests that the increased blood flow because of high cardiac output seen in chronic liver disease causes pulmonary vascular wall shear stress, which triggers the dysregulation of vasoactive, proliferative, and angiogenic mediators, eventually leading to changes in the arterial wall characteristic of POPH. Another proposed mechanism includes an imbalance of vasoactive substances and portosystemic shunting leading to the increased vasoactive and proliferative agents reaching the lung vasculature.

### Epidemiology

### Clinical Features of HPS

Although HPS is most commonly seen in children with portal hypertension and cirrhosis, it may also occur in patients with noncirrhotic portal hypertension (including focal nodular hyperplasia and nodular regenerative hyperplasia), acute and chronic hepatitis, acute liver failure, and vascular abnormalities that limit hepatic venous outflow to the lungs.

![Figure 1](image_url). Pathophysiology of POPH and HPS. In POPH, progressive remodeling of the wall of small pulmonary arteries with vasoconstriction and thickening of the arterial wall leading PAH and right heart failure. In HPS, IPVD leads to effective intrapulmonary arterial shunting and hypoxemia.

### Table 1. Diagnostic criteria for HPS and POPH

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>Advanced liver disease (most common), portal hypertension, CPSSs, IPVD: a positive contrast-enhanced transthoracic echocardiogram: presence of microbubbles in the left heart ≥3 cardiac cycles after right heart microbubbles following 10 mL agitated saline injection in a peripheral vein. Abnormal arterial oxygenation: hypoxemia (PAaO2 ≥15 mm Hg). Presence of portal hypertension: either a clinical diagnosis, such as gastroesophageal varices, splenomegaly, ascites, or elevated portal pressure confirmed by hemodynamic measurement. Plus. Right heart catheterization showing: mPAP &gt;25 mm Hg, PVR &gt;3 wood units, Normal PAWP &lt;15 mm Hg.</td>
</tr>
<tr>
<td>POPH</td>
<td>Presence of portal hypertension: either a clinical diagnosis, such as gastroesophageal varices, splenomegaly, ascites, or elevated portal pressure confirmed by hemodynamic measurement. Plus. Right heart catheterization showing: mPAP &gt;25 mm Hg, PVR &gt;3 wood units, Normal PAWP &lt;15 mm Hg.</td>
</tr>
</tbody>
</table>

Some patients may be asymptomatic during the early stage of the disease. Typical symptoms include dyspnea on exertion or at rest (Table III; available at www.jpeds.com). Dyspnea upon standing (platypnea) and hypoxemia exacerbated in the upright position (orthodeoxia) may be seen in about 25% of patients. Fatigue, digital clubbing, cyanosis, and diffuse telangiectasias are seen in advanced disease.

Prevalence of HPS
The reported prevalence of HPS depends on the at-risk patient group studied. Generally, it is more prevalent in children with cirrhosis (Table II). The studies on HPS shown in Table II have different inclusion criteria and definition of HPS, and variable methods of assessment. They also suffer from ascertainment bias, leaving it open as to the true prevalence of HPS in children with chronic liver disease.

(cavopulmonary shunts, Abernethy malformation). Some patients may be asymptomatic during the early stage of the disease. Typical symptoms include dyspnea on exertion or at rest (Table III; available at www.jpeds.com). Dyspnea upon standing (platypnea) and hypoxemia exacerbated in the upright position (orthodeoxia) may be seen in about 25% of patients. Fatigue, digital clubbing, cyanosis, and diffuse telangiectasias are seen in advanced disease.

Figure 2. Pathogenesis of HPS. In both laboratory animal model (common bile duct ligation [CBDL] in rats) of HPS and bacterial translocation commonly seen in liver cirrhosis, increased production of endothelin-1 (ET-1), a potent vasoconstrictor derived from the cholangiocyte, and tumor necrosis factor (TNF) activate the nitric oxide synthases (NOS), which include endothelial NOS (eNOS) and inducible NOS (iNOS). This in turn leads to an increased production of nitric oxide (NO), a potent vasodilator. Activated eNOS also results in overexpression of endothelin B receptor in the pulmonary vascular endothelium. Second, both bacterial translocation, which is more commonly seen in cirrhosis, as well as endotoxia, attract macrophages to the pulmonary vasculature. Monocytes express inducible NO synthase (and produce NO) and produce heme oxygenase-1, leading to carbon monoxide generation, both of which further exacerbate pulmonary vasodilatation. Finally, pulmonary angiogenesis, promoted by vascular endothelial growth factor (VEGF) signaling and production of CX3CL1, is also an important contributor of pulmonary vascular changes seen in HPS. VEGF is produced by the macrophages accumulating in the pulmonary vasculature and is also important in expressing iNOS and producing heme oxygenase-1. Akt, protein kinase B; CBDL, common bile duct ligation; CO, carbon monoxide; CX3CL1, chemokine fractalkine membrane bound; CX3CR1, Chemokine fractalkine receptor; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated protein kinase; ET-1, endothelin-1; ETa, endothelin B receptor; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TNF-a, tumor necrosis factor alpha; VEGF-A, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor.
Clinical Features of POPH

Initial symptoms of POPH are subtle, and patients may remain asymptomatic at diagnosis despite advanced disease (Table III). Clinical symptoms include signs of portal hypertensive gastropathy and those of hypoxemia with right heart failure and include shortness of breath, fatigue, chest pain, syncope, and peripheral edema (Table III). In severe disease, there may be dyspnea at rest and eventual sudden death.

Prevalence of POPH

In adults with cirrhosis and portal hypertension, the prevalence of POPH is much lower than HPS. An autopsy-based study found the prevalence to be 0.73% in patients with cirrhosis, and in another study of patients being evaluated for liver transplantation, the prevalence was 5%. In children, the prevalence of POPH is not known, and the disease has largely been reported as case series. A systematic review by Ecochard-Dugelay et al reported that POPH was present in 0.5% of children with portal hypertension and 0.9% of children with end-stage liver disease awaiting liver transplantation. Seventy-six of the 98 pediatric patients (78%) with POPH reported in the literature had advanced chronic liver disease, and the remaining 22 patients (22%) had CPSS.

Screening and Diagnosis

Screening for HPS

In adult patients, pulse oximetry with O₂ saturation <96% is sensitive and cost-effective in identifying patients with hypoxemia (arterial partial pressure of oxygen [PaO₂] <70 mm Hg) at sea level. In children with cirrhosis, however, hyperemic arterIALIZED capillary blood gas examination may be a better screening tool for HPS (Table III), although the majority of pediatric centers screen with pulse oximetry. Most experts recommend screening children either being evaluated for or already listed for liver transplantation. It is less clear which children with compensated cirrhosis and portal hypertension, CPSS, and extrahepatic portal vein obstruction require screening with pulse oximetry or arterialized capillary blood gas, and the interval for repeated screening.

Diagnosis of HPS

To confirm the diagnosis of HPS, it is essential to confirm presence of hypoxemia by capillary blood gas analysis and to demonstrate IPVD. The ILTS Practice Guidelines recommend using noninvasive testing to detect right to left intrapulmonary shunting such as contrast-enhanced transthoracic echocardiography (Table I), which takes into account the fact that the normal diameter of the lung vascular capillaries is <8 μm. Agitated saline creates microbubbles >10 μm in diameter that normally do not pass through the pulmonary capillary bed and do not appear in the left heart during TTE. Appearance of intravenously injected microbubbles in the left heart 3 or more cardiac cycles after visualization in the right heart is associated with abnormal vascular dilation of intrapulmonary capillaries. Intrahepatic shunting (ie, because of persistent foramen ovale or atrial septal defect) yields early microbubble appearance in the left heart within 1-2 cardiac cycles, and may make diagnosis of HPS more challenging. The more invasive (and less available) test, ⁹⁹mTc macroaggregated albumin lung perfusion scanning, may also be used. One study suggests good sensitivity even with mild degrees of IPVD in children. However, it cannot differentiate intracardiac from intrapulmonary shunting. The severity of HPS is graded as mild (PaO₂ ≥80 mm Hg), moderate (PaO₂ = 60-79 mm Hg), severe (PaO₂ 50-59 mm Hg), and very severe (PaO₂ <50 mm Hg). If a concomitant primary lung disease is thought to be contributing to hypoxemia, then a lung perfusion scan is necessary.

Screening for POPH

In candidates being evaluated for liver transplantation or transjugular intrahepatic portosystemic shunting, or children with chronic liver disease or CPSS and with suspected concomitant POPH, transthoracic Doppler echocardiography (TDE) for detection of PAH is a good screening test. However, it may underdiagnose PAH if there is no tricuspid jet present. A prospective study in adults being evaluated for liver transplantation using pulmonary artery systolic pressure >30 mm Hg had a negative predictive value of 100%, but the positive predictive value was only 59% for PAH. Most authorities recommend that a right ventricular systolic pressure on TDE >50 mm Hg or the presence of right ventricular hypertrophy or dysfunction should trigger a right heart catheterization to measure hemodynamics and evaluate for PAH. The age at which screening for POPH is indicated is not well defined, although POPH has been reported in children as young as 2.5 years of age. The American Association for the Study of Liver Diseases recommends that all patients being evaluated for liver transplantation undergo TDE to screen for POPH.

Diagnosis of POPH

To confirm the diagnosis of POPH, it is essential that PAH is demonstrated by cardiac catheterization of the right heart chambers. At present, there is no clear consensus for the right heart pressure cut-off and other criteria from Doppler echocardiography that would indicate need for right heart catheterization. Proposed criteria include the presence of right ventricular hypertrophy and right ventricular systolic pressure >50 mm Hg on Doppler echocardiography. The Joint Task Force stratifies the severity of POPH based on mPAP into mild (mPAP 25-35 mm Hg), moderate (mPAP 35-49 mm Hg), and severe (mPAP ≥50 mm Hg), and the ILTS guideline uses 35-45 mm Hg to define moderate and >45 mm Hg to define severe POPH. It is equally important to realize that not all PAH in children with liver disease is POPH, as portal hypertension is one of the many conditions leading to PAH.

Therapeutic Approaches

Therapy of HPS

HPS is associated with a significant increase in morbidity and mortality. At present, there are no specific effective medical
therapies (Table IV). General measures include providing symptomatic relief, improving quality of life and exercise capacity, and to facilitate liver transplantation if indicated. In patients with chronic hypoxemia and PaO$_2$ <60 mm Hg, continuous supplemental oxygen to maintain O$_2$ saturation above 88% is indicated because chronic hypoxemia impairs quality of life and may contribute to mortality in HPS. Although both nitric oxide and carbon monoxide have been implicated in the pathogenesis of HPS, clinical trials targeting these pathways, including ET-1 receptor antagonists or angiogenesis inhibitors, have been disappointing as no clear benefit has been shown in human trials. Somatostatin, almitrine, indomethacin, norfloxacin, inhaled nitro-L-arginine methyl ester, aspirin, and plasma exchange have all been used in small studies but without clear benefit.

Similarly, invasive interventions such as creation of transjugal intrahepatic portosystemic shunting to lower the portal venous pressure and coil embolization have been used, but the effects are variable. Ligation of CPSS in Abernethy malformation, a rare condition associated with HPS, has resulted in resolution of HPS.

Medical Therapy of POPH
β-blockers, often used in patients with cirrhosis and esophageal varices, may impair the exercise capacity of patients with POPH. Therefore, the risk-benefit of β-blockers should be considered carefully in patients with POPH and other means of treating varices (eg, endoscopic band ligation) should be considered. Anticoagulation may similarly pose a significant risk if gastrointestinal varices are present, thus it is usually avoided in POPH. Calcium channel blockers are ineffective in POPH and may elevate portal pressures and reduce right ventricular function, thus, they are contraindicated. Over the past decade, a number of new therapeutic agents for PAH have become available and used in patients with POPH (Table IV). Prostacyclin analogues possess vasodilator, antithrombotic, and antiproliferative activities but with potential side effects including worsening splenomegaly and thrombocytopenia. Activation of endothelin receptors (ET$_A$ and ET$_B$) leads to pulmonary vasoconstriction. Thus, endothelin receptor antagonists, such as bosentan, ambrisentan, and macitentan, have reduced PAH and resulted in improved exercise tolerance if there is no hepatotoxicity (ie, aspartate aminotransferase and alanine aminotransferase remain in an acceptable range). Phosphodiesterase-5 inhibitors, such as sildenafil, tadalafil, and vardenafil, increase cyclic guanosine monophosphate and inhibit the growth of pulmonary vascular smooth muscle cells and are effective in lowering pulmonary vascular resistance. All have excellent side effects profiles and have been used successfully to lower the mPAP to allow for eventual liver transplantation. Nevertheless, most of the reports on the use of these agents are either case reports or single-center studies. No formal trials in children with POPH of any of these agents have been conducted.

Surgical Management of POPH
Survival is poor among children with POPH without medical therapy. In pediatric POPH associated with CPSS, closure of

<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>Class (examples)</th>
<th>Mechanism(s) of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS General measures</td>
<td>Supplemental oxygen if PaO$_2$ &lt;60 mm Hg to maintain oxygen saturation &gt;88%</td>
<td>Lowering of portal pressure Complete resolution or significant improvement</td>
<td>Variable effect, benefit uncertain Indicated if PaO$_2$ &lt;60 mm Hg Contraindication: if preliver transplantation PaO$_2$ &lt;45-50 mm Hg, increased morbidity &amp; mortality. But outcomes maybe center-specific.</td>
</tr>
<tr>
<td>Invasive measures Liver transplantation</td>
<td>TIPS</td>
<td>Lowering of pulmonary vascular resistance by causing pulmonary vasodilatation by inhibiting PDE-5 enzyme and inhibiting the growth of pulmonary vascular smooth muscle cells</td>
<td>Most are case reports or series in adult population. No formal trials in children with POPH have been conducted.</td>
</tr>
<tr>
<td>POPH Medical therapies</td>
<td>Prostacyclin analogues (epoprostenol, inhaled treprostinil, inhaled iloprost)</td>
<td>Vasodilator, antithrombotic, antiproliferative activities</td>
<td>Report of improvements in hemodynamics mainly in case reports. A single-center study reported an improved 5-year survival using intravenous prostacyclin. Inhaled treprostinil now most commonly used in the US Oral ERAs are most commonly used in PPHP. Reported hepatotoxicity because of bosentan in advanced cirrhosis. Less hepatotoxicity in ambrisentan, macitentan. Sildenafil improves exercise tolerance and has an excellent side effect profile. Tadalafil and vardenafil are long-acting agents with good side effects profile and advantage of ease in administration.</td>
</tr>
<tr>
<td></td>
<td>ERAs (bosentan, ambrisentan, macitentan)</td>
<td>Blocking of endothelin receptors, which upon activation leads to pulmonary vasoconstriction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDE-5 inhibitors (sildenafil, tadalafil, vardenafil)</td>
<td>Lowering of pulmonary vascular resistance</td>
<td></td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td></td>
<td>Indication: Liver transplantation is not an indication for POPH per se without other indications for liver transplantation. Contraindication: liver transplantation is contraindicated in patients with mPAP &gt;45-50 mm Hg that is unresponsive to medical therapies</td>
</tr>
</tbody>
</table>

ERA, endothelin receptor antagonists; PDE-5, phosphodiesterase-5; TIPS, transjugular intrahepatic portosystemic shunt.
the shunts either surgically or via interventional radiology, is indicated.2 Ecocard-Dugelay et al reviewed 22 cases of POPH in patients with CPSS reported in the literature,6 of whom had closure of the shunt either via radiological intervention or surgically, and were alive after a median follow-up of 3 (0.5-14) years.2 However, the response of mPAP after shunt closure was mixed.2 Some were also treated with vasodilators, and 3 eventually had liver transplantation.2

Role and Timing of Liver Transplantation

Liver transplantation in children with chronic liver disease complicated by HPS or POPH may be curative and life-saving. However, the presence of these pulmonary vascular complications increases the risks of liver transplantation.

Indications for Liver Transplantation in HPS

Liver transplantation reverses the intrapulmonary vascular shunting and hypoxemia present in HPS over a variable period of time. Previously, liver transplantation was considered as contraindicated in children if HPS-related hypoxemia was severe (PaO2 <60 mm Hg).36 However, the poor outcome of patients with HPS without liver transplantation, as well as improved outcome and resolution of HPS after liver transplantation reported since the 1990s, has led to a re-evaluation of the role of liver transplantation in HPS.37 Thus, progressive hypoxemia (PaO2 <60 mm Hg) because of HPS, which responds poorly to medical management, is now considered as an indication for liver transplantation.7 Liver transplantation results in complete resolution of gas exchange abnormalities in the vast majority of patients with HPS.

Contraindications for Liver Transplantation in HPS

Very severe hypoxemia (PaO2 <50 mm Hg) increases the risk for complications and mortality after liver transplantation.5 However, an adult series which included 70 patients with HPS, 34 of whom had severe HPS, who underwent liver transplantation in 2 experienced centers showed no increased mortality with very severe HPS and a postliver transplantation mortality rate of only 6%, suggesting that excellent outcomes are achievable in experienced centers.38 However, there are other indications for liver transplantation. For patients on therapy, pulmonary arterial pressures should be rechecked before or at the beginning of liver transplantation to ensure continued response of mPAP. Patients with mild-to-moderate POPH who had met criteria for liver transplantation should be considered good candidates. However, severe unresponsive disease remains a contraindication.

POPH has significant mortality.2,42-45 Ecocard-Dugelay et al reviewed 98 children with POPH reported in the literature, 18 (18%) of whom had undergone liver transplantation (median age at liver transplantation 12 years; range 2.5-40 years, 14 before 18 years of age).2 There were 5 (29%) postoperative deaths; 4 were early deaths related to right heart failure.2 Nine patients had preliver transplantation vasodilator therapy, resulting in reduction of mPAP. Of those who were alive at the time of report, a majority had an improvement in mPAP after liver transplantation.7 Clear criteria indicating which patients with POPH would benefit the most from liver transplantation have not been developed.

All studies have shown that mortality postliver transplantation in POPH remains high in patients with severe PAH, with the majority of deaths occurring early following liver transplantation and related to right heart failure and PAH.24 Thus, identifying POPH early in its course in patients with advanced liver disease through standardized screening may allow for earlier initiation of POPH vasodilator therapy and consideration for liver transplantation before severe PAH precludes transplantation. Weaning of POPH medications post-transplant is a clinical decision for which there are no guidelines, but should done gradually; approximately 50% of patients can be weaned off of preliver transplantation POPH medications postliver transplantation over weeks to months.

Contraindications of Liver Transplantation in POPH

In children with POPH and with a mPAP of >45-50 mm Hg that cannot be lowered by vasodilator therapy, liver transplantation remains contraindicated.5

Future Research Priorities

Both HPS and POPH carry significant morbidity and mortality. Because both are rare but serious complications of chronic Hepatopulmonary Syndrome and Portopulmonary Hypertension in Children: Recent Advances in Diagnosis and Management
liver disease, current knowledge in pediatric HPS and POPH is mainly based on case reports or small series. Thus, the current treatment of these conditions is extrapolated from that in adults and is not sufficiently evidence based. It is, therefore, suggested that a multicenter, multinational registry be developed for childhood HPS and POPH. The diagnostic criteria for both conditions should be clearly defined and uniformly applied to assist in standardized phenotyping of HPS/POPH, and development of a prognostic risk score based on the severity of liver dysfunction, coexisting lung conditions, degree of hypoxemia, and hemodynamics. The role of liver transplantation in both conditions needs to be more clearly defined, and applied to update the pediatric end-stage liver disease and model for end-stage liver disease exception criteria for children. Prospective, multicenter drug trials should also be initiated involving children with both conditions. Defining the role for postliver transplantation extracorporeal membrane oxygenation in those with severe HPS and for PAH susceptibility genotype screening in those with POPH are other areas that need refinement.

Conclusions

HPS and POPH are rare but serious complications of advanced liver disease, cirrhosis, and portosystemic shunting. Currently, available pharmacotherapy for both conditions is not satisfactory. POPH secondary to CPSS should be treated by eliminating the shunt either surgically or via radiologic intervention. Liver transplantation is indicated in children with HPS if the PaO₂ is 50-60 mm Hg and cautiously instituted with PaO₂ <50 mm Hg. Liver transplantation is not indicated for POPH alone without other criteria for liver transplantation but can be considered in mild-to-moderate POPH. In moderate POPH, liver transplantation remains a risky procedure and aggressive therapy to reduce PAH is necessary if liver transplantation is indicated. In severe POPH with end-stage liver disease, liver transplantation is contraindicated. If liver transplantation is considered, early aggressive therapy with pulmonary vasodilator therapy at an experienced center should be initiated. Early screening for HPS and POPH in patients at risk should be of benefit, however, the age and intervals for such screening have not been established. A prospective multicenter registry with uniform diagnostic criteria is needed to clarify the true prevalence, natural history, and prognostic factors of both conditions in children. The role of liver transplantation in both conditions needs further clarification.

References


Table II. Prevalence of HPS in selected series

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Setting</th>
<th>N</th>
<th>Definition</th>
<th>Methods of assessment</th>
<th>% with HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noli et al(^{12})</td>
<td>2008</td>
<td>Children with liver disease, cirrhosis and portal hypertension</td>
<td>N = 26 (18 had liver cirrhosis and portal hypertension, 8 had oxygen saturation &lt;97% in a cohort of 301 children with mild liver disease)</td>
<td>CEE showing IPVD Hypoxemia (PaO(_2) &lt;70 mm Hg), PAaO(_2) ≥ 15 mm Hg</td>
<td>• CEE (positive if present in the left side within 3 cardiac cycles); • Technetium-99m macroaggregated albumin scintigraphy</td>
<td>27% (n = 8) had IPVD; 8% (n = 2) hemet criteria for HPS</td>
</tr>
<tr>
<td>Whitworth et al(^{15})</td>
<td>2010</td>
<td>Children with stable liver cirrhosis, extrahepatic portal hypertension</td>
<td>N = 33 (cirrhotic = 28; extrahepatic portal hypertension = 5)</td>
<td>CEE showing IPVD Hypoxemia (SaO(_2) ≤ 92%)</td>
<td>• CEE (positive if present in left side within 3-6 cardiac cycles) • Agitated saline</td>
<td>18% (n = 6) had IPVD; 3% (n = 1) had HPS</td>
</tr>
<tr>
<td>Sasaki et al(^{16})</td>
<td>2010</td>
<td>Children with biliary atresia</td>
<td>N = 88</td>
<td>CEE showing IPVD</td>
<td>• CEE (positive if present in the left side within 3-6 cardiac cycles)</td>
<td>9.1%</td>
</tr>
<tr>
<td>Deghanni et al(^{17})</td>
<td>2010</td>
<td>Children with advanced liver disease awaiting liver transplantation</td>
<td>N = 79</td>
<td>CEE showing IPVD Hypoxemia (PaO(_2) &lt;70 mm Hg)</td>
<td>• CEE (positive if present in the left side within 4 cardiac cycles)</td>
<td>11.4% (n = 9)</td>
</tr>
<tr>
<td>Sari et al(^{18})</td>
<td>2011</td>
<td>Children with portal hypertension</td>
<td>N = 40 (cirrhotic = 24, noncirrhotic = 16)</td>
<td>CEE and/or scintigraphy showing IPVD Hypoxemia (PaO(_2) &lt;80 mm Hg) and/or PAaO(_2) ≥15 mm Hg</td>
<td>• PAaO(_2) • CEE (positive if present in the left side within 4-6 cardiac cycles) • Technetium-99m macroaggregated albumin scintigraphy</td>
<td>10% (n = 4). All 4 cases of HPS occurred in the cirrhotic group.</td>
</tr>
<tr>
<td>Borkar et al(^{12})</td>
<td>2014</td>
<td>Children with portal hypertension</td>
<td>N = 135 (cirrhosis = 35, extrahepatic portal venous obstruction = 100).</td>
<td>CEE showing IPVD Hypoxemia: either 1 of the following: PaO(_2) &lt;80 mm Hg; PAaO(_2) ≥15 mm Hg; fall in PaO(_2) ≥5% or ≥1 mm Hg from supine to standing position</td>
<td>CEE (presence of microbubbles in left side within 4-6 cardiac cycles)</td>
<td>Overall 20% (n = 27); 40% (n = 14) in the cirrhotic group; 13% (n = 13) in the extrahepatic portal venous obstruction group.</td>
</tr>
</tbody>
</table>

CEE, contrast-enhanced echocardiography; PAaO\(_2\), alveolar-arterial oxygen gradient.

Table III. Clinical features, screening, and diagnosis of HPS and POPH\(^{\dagger}\)

<table>
<thead>
<tr>
<th>Variables</th>
<th>HPS</th>
<th>POPH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Documented</td>
<td>Documented</td>
</tr>
<tr>
<td>Screening advised</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Correlation with liver disease severity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Occurrence in adults and children</td>
<td>Common: liver cirrhosis (biliary atresia, chronic hepatitis, autoimmune hepatitis, etc.)</td>
<td>Less common in children; 75% associated with chronic liver disease or EHPVO, 25% associated with CPSS(^{1})</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPVD leading to effective intrapulmonary arterial shunting and hypoxemia</td>
<td>Increased pulmonary vascular resistance and remodeling leads to progressive PAH and right heart failure</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Related to hypoxemia: dyspnea on exertion and at rest, platypnea, orthodeoxia</td>
<td>Symptoms of right heart failure: shortness of breath, peripheral edema, gallop</td>
</tr>
<tr>
<td>Severe hypoxemia (PaO(_2) &lt; 50 mm Hg)</td>
<td>Common</td>
<td>Doppler echocardiography (pulmonary arterial systolic pressure &gt;30 mm Hg)</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Hyperemic arterialized capillary blood gas or pulse oximetry (PaO(_2) &lt;70 mm Hg)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung biopsies needed for diagnosis</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ABG required for diagnosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>High cardiac output only</td>
<td>Flow obstruction</td>
</tr>
<tr>
<td>Confirmation of diagnosis</td>
<td>CE-TTE</td>
<td>RHC</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor 5-y survival if not treated</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indication for liver transplant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Resolution after transplant</td>
<td>Common</td>
<td>Variable</td>
</tr>
</tbody>
</table>

ABG, arterial blood gas; CE-TTE, contrast-enhanced transthoracic echocardiographic; EHPVO, extrahepatic portal venous obstruction; RHC, right heart catheterization.
